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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,864	LUKYANOV ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10-14 and 17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/02, 9/10/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's election with traverse of Group I (claims 1-9 and 15-16) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 10-14 and 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention.

2. The Preliminary Amendment filed on June 19, 2002 has been received and entered.

Specification

3. The specification is objected to because of the following informalities:

(a) The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as FACSVANTAGE ™ , ADVANTAGE®, VACUTAINER ™ , for example, have been noted in this application (see pages 33-34 and 38). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

(b) The specification is also objected to because on page 38 the sequence "MRHHHHHHGS" is disclosed without a specific sequence identifier.

(c) On page 6 of the specification appears "as well as the proteins encoding the same" (see line 32), and proteins do not encode.

(d) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Nucleic Acids Encoding Non-Aggregating Fluorescent Proteins and Methods For Using Same".

Correction of the above and compliance with the sequence rules is required.

Drawing

4. The drawings filed on February 20, 2002 have been accepted by the examiner.

Claim Objection

5. Claims 1-4, 6-7, 9 and 15-16 are objected to because of the following informalities:

Claims 1-3 are objected to because the species name in the claims is not italicized, for example *Cnidarian*.

Claim 4 is objected to because the claim recites "residues" in association with nucleic acid sequences instead of "nucleotides". Note that "residues" is an art-recognized term associated with amino acids.

For clarity claim 6 should be amended to recite "a construct comprising a vector and the nucleic acid according to claim 1", instead of "a nucleic acid" (see also claim, 4, 7(b), 15-16).

Claim 9 is objected to for the recitation of "and/or", for clarity the claim should recite only one term (see for example claim 1).

Correction of the above is required.

Information Disclosure Statement

6. The Information Disclosure Statements filed on June 19, 2002 and September 10, 2002 have been received and entered. The references cited on the PTO-1449 Forms have been considered by the examiner and a copy is attached to the instant Office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

7. Claims 1-9 and 15-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 and the dependent claims hereto are drawn to a nucleic acid, which reads on a product of nature. The claims should be amended to indicate the hand of the inventor, for example the insertion of isolated or purified in connection with the nucleic acid to identify a product not found in nature (see MPEP 2105).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-9 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a nucleic acid that encodes a non-aggregating chromo or fluorescent mutant, however, the claimed nucleic acid is only defined by a function (encoding a protein) not a structure see for example claims 1-3, 5-9 and 16-15. In addition, the encoded protein is a mutant of an aggregating *Cnidarian* chromo or fluorescent protein or mutant thereof (see for example claim 1) and the claim does not define a reference point for the mutation as the protein is defined solely by its properties. It is noted that on page 2 of the instant specification it is disclosed that the "non-aggregating feature arises from the modulation of residues in the N-terminus of the protein and the chromo or fluorescent feature arises from the interaction of two or more residues of the protein" (see lines 10-12 of page 2). It is further stated on page 9 of the instant specification that "the non-aggregating polypeptides of the present invention have amino acid sequences that differ from their corresponding wildtype sequences by a mutation in the N-terminus... more specifically basic residues Lys and Arg located near the N-

termini of the proteins are substituted (see lines 33-39 of page 9). However, the claims encompass a genus of non-aggregating mutants and aggregating mutants thereof not adequately described in the instant specification. For example, on page 16 of the instant specification it is stated that "the sequence changes may be substitutions, insertions, deletions or a combination thereof. Deletions may further include larger changes, such as deletions of a domain or exon, for example stretches of 10, 20, 50, 75, 100, 150 or more amino acid residues" (see lines 30-33). Additionally, the source of the non-aggregating mutant might be an aggregating protein already mutated, however, the instant specification does not indicate whether the non-aggregating properties recited in the claims are retained when the encoded protein is subjected to the modifications contemplated. Therefore the parental mutants thereof and the non-aggregating mutants encompass a large genus of mutants.

It is noted that on page 38, Table 1 provides wildtype and mutated *Anthozoan* proteins (parental aggregating proteins) and Table 2 on pages 39-40 provides mutated non-aggregating proteins, which exemplifies point mutations and single deletions. However, the claims encompass mutations other than point mutations or single deletions which have not been described, therefore, the specification fails to provide a representative number of species for the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. Note that on page 10 of the specification it is disclosed that by N-terminus is meant within about 50 residues from the N-terminus, often within about 25, etc. Further on page 13 at lines 15-17 it is stated that the proteins can contain 25 amino acids, 50 amino acids, 75 amino acids, 100 amino acids or more, which means that an N-terminus having 50 residues can

be subjected to mutations wherein Arg or Lys is substituted by any or all neutral or negative residue, which could produce an enormous amount of mutants. Moreover, although the specification indicates that basic residues Lys and Arg will be substituted with negatively charged or neutral residues, the instant specification does not describe all possible mutations such as plural substitutions. It is noted that Table 2 provides examples such as R2A, K5E and K9T, however, this is not a representative number of species, as the claims encompasses mutations such a R2 replaced by all the possible neutral and negative residues, or other combinations such as R2A-E-T . Therefore, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptide mutants.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In addition, the claims encompass a large genus of nucleic acids, which are not adequately described, see for example claims 4 and 5. Note that claim 4 recites a sequence that is substantially identical to at least 10 nucleotides of the claimed nucleic acid sequences and they do no have to be contiguous. Further, the specification on page 12 state that "substantially the same means at least about 60%, 75%, 80% etc., (see lines 15-17) which includes a large amount of variation. Additionally, claim 15 is directed to an application that employs the nucleic acid,

and the claim encompasses any and all possible applications, which have not been described by the instant specification.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid and the encoded polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 1-9 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid set forth in SEQ ID NOS: 14, 15, 17, 19, 21 and 23, and information provided in Tables 1 and 2 (see pages 38-40 of the specification), does not reasonably provide enablement for any non-aggregating mutant or any aggregating

mutant thereof or any nucleic acid fragment or any application employing the nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of parental aggregating mutants and non-aggregating mutants. Additionally, claims are directed to the parental mutants that produce non-aggregating mutants (double mutants). Further, non-aggregating mutants are said to arise from the modulation of residues in the N-terminus (which can span 50 residues) for proteins that can have 50 or 100 or more residues, see pages 2, 10 and 13 of the instant specification. The parental mutants thereof are said to arise from for example, the following wildtypes: amFP485, cFP484, zFP506, zFP540, drFP585, dsFP484, asFP600, dgFP512 (see page 10), however, there is no indicia as to how much modifications can be tolerated in the wildtype structures. The claims encompass mutations that are not exemplified in the tables on pages 38-40. It is noted that the

tables reflect for example point mutations, wherein basic residues are replaced, however, the claims also encompass mutations such as Lys or Arg replaced by for example, a tri-peptide or octapeptide consisting of negatively charged or neutral amino acid residues as the instant specification does not limit the amount of residues that can be used to replace the basic residues or enumerate all the positions the replacements can occupy. Moreover, in view of the language of claim 4, "substantially the same as", the claimed protein may not be a non-aggregate mutant. Note that the instant specification on page 12 indicates that "substantially the same as" means 60% or 75% etc., thus, a large amount of variability is allowed.

The specification on page 9 (see lines 33-35) discloses that the non-aggregating polypeptides of the present invention have amino acid sequences that differ from their corresponding wild type sequences by a mutation in the N-terminus that modulates the charges appearing on side groups of the N-terminus residues, i.e. to reverse or neutralize the charge, in a manner sufficient to produce a non-aggregating mutant of the naturally occurring protein or aggregating mutant thereof (emphasis added). However, the "so called manner sufficient to produce a non-aggregating mutant" is not discussed. It is noted that on pages 8-9 decreased aggregation is discussed, however, the instant specification does not set forth for example, the specific environment such as the solution needed to achieve the properties claimed. The chromo or fluorescent protein once modified to achieve non-aggregation may not function as anticipated as it may not have the same properties of the native/wild-type protein or mutant thereof.

The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified based on the changes contemplated on page 16, for example, or if said protein will be functional or exhibit the same properties or characteristics as

the wildtype or parental mutant thereof. In the instant application, the properties of the protein recited in the claims (see for example claim 1) and recitation of a nucleic acid encoding such is insufficient to determine a chemical structure for the mutants encompassed in the claims (see claims 1-3, 5-9 and 16-15). Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Further, the claims recite the use of the nucleic acid in an application (see for example claim 15), however, there is no limitation as to what type of application is intended by the claimed invention, which is not supported by the instant specification. Therefore, the claims encompass fragments (claims 4-5) and mutants (claim 1) that may not have any biological activity or display the desired properties. It is noted that claim 4 recites the structure missing from for example claim 1, however, the phrase "substantially the same as" broadens the scope and based on the definition provided in the instant specification (see page 12), one of skill in the art would have to engage in undue experimentation to construct an aggregating mutant thereof and then produce from this a chromoprotein or fluorescent mutant that maintains the recited properties. Due to the large quantity of experimentation necessary to generate the infinite number of mutants/fragments recited in the claims and possibly screen same for activity/desired properties and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are

conserved and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity/properties comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. It is noted that the instant specification provides for example point mutations, however, the claims encompass plural substitutions, which are not exemplified, nor are there examples of all the possible neutral residues in a mutant sequence. Furthermore, the parental sequence can be a mutant of the wildtype subjected to further mutation to form the non-aggregating mutant. The skilled artisan would recognize the high degree of unpredictability that all the fragments/mutants encompassed in the claims would retain the recited properties.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). Therefore, amino acid substitutions are critical to the protein's structure/function relationship. Moreover, the amino acid residues of the claimed invention are substituted to reverse or neutralized the charge appearing on side groups of the N-terminus residues to obtain the non-aggregating mutant, however, the environment that the protein is in, is also critical. It is well known in the art that aggregation can be induced by changes in pH, the salt concentration, valency of ions or the polarity of the solvent, however, the instant specification does not provide any guidance with regard to these factors that can critically affect aggregation, to breathe life into the claims. For example, Lund et al. (Biophysical Journal, vol. 85, no. 5, November 2003, pages 2940-2947) state that solution conditions can prevent or promote aggregation, such as salt concentration, ion valency, pH and or solvent (see page 2940).

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's

sequence and result in certain activity/property, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed mutants as the claims encompass mutants not described in the instant specification. Thus, one of skill in the art would have to engage in undue experimentation to construct the mutants of the claimed invention and examine the same for function/the specific properties.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of mutants/fragments. The claims broadly read on any aggregated mutant thereof or any non-aggregated mutant of said aggregated mutant or any nucleic acid fragment/application. The claims also read on any nucleotide sequence that is "substantially the same as the given sequences (SEQ ID NO: 14, 15, 17, 19, 21 and 23). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and

undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, the instant specification to be enabling need to provide direction/guidance regarding whether the structure of the chromo or fluorescent mutant can tolerate the modifications encompassed by claims and still possess the desired properties or whether a protein that does not have the desired properties may result. Absent sufficient guidance/direction one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and insufficient working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test mutants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible mutants to find one that has the desired properties as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 5, 9 and 15 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

(a) Claim 5 lack antecedent basis as independent claim 1 does not provide a "process for selecting a fragment of the nucleic acid".

(b) Claim 9 is indefinite for the recitation of "substantially free", as the term is not defined in the instant specification and it is unclear what quantity to associate with the term. Is the resultant protein 50% free of other proteins? What quantity is or is not substantial?

(c) Claim 15 is indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. Note that the claim recites" In an application that employs a nucleic acid encoding chromo- or fluorescent protein", and the claim does not include or exclude the types of application.

Basis For NonStatutory Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-3, 5-8 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 8-10, 12-15, 16 (a and d), 17, 20 (a, b, d and e), 21, 22-23 and 31(claim 30 will be renumbered as claim 31) of copending Application No. 10/006,922. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). *See In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).* Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claims 1-3, 5-8 and 16 are directed to a nucleic acid that encodes a non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof, from a non-bioluminescent *Cnidarian* species that is *Anthozoan*, nucleic acid fragments, a construct comprising a vector, an expression cassette, a cell

or progeny and a kit. The copending application claims 1-5, 8-10, 12-15, 16 (a and d), 17, 20 (a, b, d and e), 21, 22-23 and 31 are directed to a nucleic acid present in other than its natural environment that encodes a chromo- or fluorescent protein and mutant proteins from a non-bioluminescent *Cnidarian* species which is *Anthozoan* or a non-*Pennatulacean Anthozoan* species, nucleic acid fragments, a construct comprising a vector, an expression cassette, cells or progeny and a kit.

The instant application claims differ because they are directed to a non-aggregating chromo/fluorescent mutant protein. The specification of the instant application indicates that the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein (see page 2 of the instant application). However, the copending application claims 12 and 14-15 are directed to mutants of the chromo/fluorescent protein encoded by the nucleic acid. Although copending claims 14 and 15 recite point mutations these are encompassed in the broad language of the instant claim 1 "mutant", as mutations can be substitutions, point mutations, frame shift, deletions, etc.

The claims in the copending application recite the language "present in other than its natural environment", which could be interpreted as isolation of the nucleic acid from the cell, or a nucleic acid that is still present in the cell but separated from the whole organism. Further, the copending application claims 3, 5 and 10 are directed to "an isolated nucleic acid", however, such could also be achieved in the present application, as methods of isolating a nucleic acid are routine in the art. Moreover, the instant claimed nucleic acid could be interpreted as naturally occurring or non-naturally occurring, hence the language recited in the copending application is encompassed in the instant claim language.

Although the instant application claims do not recite non-*Pennatulacean Anthozoan* species (see claims 4, 8, 12, 16 and 20 of the copending application) this species is encompassed in the broad recitation of *Anthozoan* recited in the instant claims. Further the instant application claims directed to a fragment of the nucleic acid, a construct, an expression cassette, a cell/progeny and a kit, couldn't be considered patentably distinct over the copending application claims, which are directed to the same subject matter. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions of a specifically defined species and since the language in the claims is similar. Thus, the instant application claims are an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-3, 5-9 and 15-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 10-14 and 19-20 of copending Application No. 10/845,484. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). *See In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).* Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claims 1-3, 5-9 and 15-16 are directed to a nucleic acid that encodes a non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof, from a non-bioluminescent *Cnidarian* species that is *Anthozoan*, nucleic acid fragments, a construct comprising a vector, an expression cassette, a cell or progeny, a method of making the encoded protein, an application using the subject nucleic acid and a kit. The copending application claims 1-4, 10-14 and 19-20 are directed to a nucleic acid encoding an interconverted mutant of a chromo or fluorescent protein, from a *Cnidarian* species that is non-bioluminescent and is an *Anthozoan* species. In addition, the copending claims are directed to fragments of the nucleic acid, a construct, an expression cassette, a cell or progeny, a method of producing the encoded protein, an application using the nucleic acid and a kit.

The instant application claims differ because they are directed to a non-aggregating chromo/fluorescent mutant protein. The specification of the instant application indicates that the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein (see page 2 of the instant application). However, note that the copending application claims 1-4 are directed to mutants of a chromo/fluorescent protein encoded by the nucleic acid. Although, the claims of the copending application are directed to "an interconverted mutant", the specification of the copending application on page 2 disclose that the chromo/fluorescent properties have been interconverted, thus an obvious variation of the present claims.

Further the instant application claims directed to a fragment of the nucleic acid, a construct, an expression cassette, a cell/progeny, a method of producing the protein, an application using the nucleic acid and a kit, couldn't be considered patentably distinct over the

copending application claims directed to the same subject matter. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions of a specifically defined species and since the language in the claims is similar. Thus, the instant application claims are an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-3, 5-9 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-10 and 17 of copending Application No. 10/806,930. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). *See In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).* Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claims 1-3, 5-9 and 16 are directed to a nucleic acid that encodes a non-aggregating chromo- or fluorescent mutant of an aggregating *Cnidarian* chromo- or fluorescent protein or mutant thereof, from a non-bioluminescent *Cnidarian* species that is *Anthozoan*, nucleic acid fragments, a construct comprising a vector, an expression cassette, a cell or progeny, a method of making the encoded protein and a kit. Copending application claims 1-2 are directed to a nucleic acid encoding a polypeptide product comprising a first and second

chromo/fluorescent domain, optionally joined by a linking domain, wherein said first and second domain associate with each other under intracellular conditions so that said encoded polypeptide assumes a tertiary structure and said first and second domains are oligomeric producing domains. In addition, the copending application claims 3-5, 7-10 and 17 are directed to *Cnidarian* species or mutants that are non-bioluminescent from *Anthozoan* species, a construct, an expression cassette, a cell or progeny, a method of producing the encoded protein and a kit.

The instant application claims differ because they are directed to a non-aggregating chromo/fluorescent mutant protein. The specification of the instant application indicates that the non-aggregating feature arises from the modulation of residues in the N-terminus of the protein (see page 2 of the instant application). However, note that the copending application claims are directed to mutants of a chromo/fluorescent protein encoded by the nucleic acid, see for example claim 3. Additionally, the two sets of claims differ as the copending claims are directed to a first and second domain optionally linked and recites other properties of the protein not present in the instant application. Note that the recited "optional" limitation is a non-limitation, as it is optional. Furthermore, the first and second domain and the recited properties are inherent to the protein, therefore, reads on claim 1 of the instant application.

Further the instant application claims directed to a fragment of the nucleic acid, a construct, an expression cassette, a cell/progeny, a method of producing the protein and a kit, cannot be considered patentably distinct over the copending application claims directed to the same subject matter. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions of a specifically defined species and since the language in the

claims is similar. Thus, the instant application claims are an obvious variation of the copending application claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art of *Record*

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lukyanov et al. (WO 01/27150, 19 April 2001, cited on IDS 9/10/02), teach a nucleic acid encoding *Anthozoa* derived chromo/fluoroporteins and mutants thereof as well as fragments of the subject nucleic acid, kits and applications that include the subject nucleic acid. The reference is relevant to the claimed subject matter, however, does not meet all the requirements necessary under 35 U.S.C. 102(e).

Tsien et al. (U.S. Patent No. 6,342,379, January 29, 2002) teach bioluminescent or naturally fluorescent proteins, however, does not teach a nucleic acid encoding a non-aggregating chromo or fluorescent mutant of an aggregating *Cnidarian* species.

Conclusion

16. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS HAR
9/20/04
Patent Examiner